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Science Policy Note SPN2017-03

Acute Dermal Toxicity Study Waiver

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1.0 Background

In December 2013, Health Canada's Pest Management Regulatory Agency (PMRA) published the *Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides*, which defined situations under which applicants and registrants could apply for a data waiver for specific acute studies.[1] The PMRA also co-led the development of an Organisation for Economic Development and Co-operation guidance document,[2] published in 2016, that further addressed data waivers for acute studies. More recently, an initiative to develop guidance on waiving acute dermal toxicity tests for pesticide formulations was undertaken under the auspices of the Canada-United States Regulatory Co-operation Council (RCC). A regulatory partnership between the PMRA and the United States Environmental Protection Agency's (USEPA) Office of Pesticide Programs on this initiative has facilitated the alignment of both countries' regulatory approaches, while advancing efforts to implement the 3Rs of animal testing, namely, to reduce, refine, or replace the need for animal studies.

In March 2017, the PMRA published PRO2017-02, a regulatory proposal regarding an acute dermal toxicity study waiver.[3] This document described the retrospective analyses undertaken by Health Canada's PMRA and its commitment, under the RCC initiative, to publish guidance that outlines the Agency's position on the use of acute oral toxicity studies as an alternate predictor of dermal hazard for the purpose of dermal hazard labelling for pesticides. Three sets of comments were received during the consultation period; responses to these comments are summarized in Appendix I of this document. No further changes were made to the regulatory proposal, which now serves as the basis for this science policy note.

2.0 Purpose

As indicated in the RCC Joint Forward Plan for this initiative, there is widespread agreement that a reduction in the number of animals used and the refinement of testing to reduce suffering should be important goals in the development and implementation of testing methods that avoid the use of live animals. The guiding principles for more judicious use of animals in testing are the Three Rs (3Rs), namely, reduce, refine and replace animal testing. These principles are now followed in many testing establishments worldwide.

The PMRA is committed to the 3Rs, wherever possible, and continues to work with regulatory partners, such as the USEPA, to validate and promote alternatives to animal testing. The PMRA has focused its current efforts on acute toxicity studies, which traditionally included a battery of

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1 Health Canada (2013). *Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides.* http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/toxicity-guide-toxicite/index-eng.php accessed February 2017.

2 Organisation for Economic Co-operation and Development (2016). Series on Testing and Assessment, No. 237. *Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests.* http://www.oecd.org/env/ehs/testing/series-testing-assessment-publications-number.htm accessed February 2017.

3 Health Canada (2017). Regulatory Proposal PRO2017-02, *Acute Dermal Toxicity Study Waiver.* http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/_pro2017-02/index-eng.php accessed April 2017

six acute animal toxicity studies for hazard characterization and labelling of pesticides (that is, acute oral, dermal and inhalation toxicity studies, eye and skin irritation studies, and skin sensitization tests). The purpose of these studies is to identify the hazard category for pesticide labelling, which in turn, influences the selection of the hazard symbol, signal words and precautionary statements on pesticide labels.

Under the RCC Joint Forward Plan, the PMRA (and USEPA) have a commitment to develop guidance on waiving acute dermal toxicity tests for pesticide formulations. The USEPA's Office of Pesticide Programs and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) conducted a retrospective analysis of oral and dermal acute lethality studies relevant to the USEPA's regulation of pesticides. On the basis of this analysis, the Office of Pesticide Programs developed a waiver guidance document pertaining to acute dermal toxicity testing for pesticide formulations (referred to as end-use products in Canada). The PMRA undertook a similar analysis from the Canadian regulatory perspective, and the results of this assessment are presented herein.

3.0 Retrospective Analysis – End-Use Products

The PMRA conducted a retrospective analysis of acute oral and dermal toxicity studies in the rat using the same dataset of 592 end-use products that was used in the USEPA analysis. The dataset comprised a range of pesticide types, including conventional pesticides, antimicrobials and biopesticides, as well as various formulation types. The USEPA dataset was used since i) it is not unusual for the same end-use products to be registered in both Canada and the United States; ii) the dataset did not have to be uniquely Canadian to demonstrate proof-of-principle; and, iii) it was an efficient means for conducting the analysis.

For each end-use product, the acute oral hazard was compared with its acute dermal hazard, based on rat LD_{50} values[4] and by utilizing both PMRA's current hazard category system as well as that of the Globally Harmonized System (GHS). The purpose of the analysis was to determine whether acute oral toxicity studies are a suitable alternative for predicting dermal hazard for labelling purposes. If so, the dermal hazard category would be deemed equivalent to that of the oral hazard category for informing the selection of labelling statements.

With regards to the PMRA category system, the oral hazard category was the same as the dermal hazard category for 417 end-use products (out of 592). The oral hazard category was lower (that is, more potent) than the dermal hazard category for 173 end-use products (out of 592). Overall, the oral hazard category was the same as, or over-predicted, the dermal hazard category for 590 (out of 592) or >99.5% of end-use products. The analysis revealed that the remaining two end-use products had a lower dermal hazard category (that is, greater potency) compared to the oral category.

[4] Lethal dose 50% (LD_{50}): the amount of the substance required to kill 50% of the test population.

The analysis utilizing the GHS category system showed similar results. A total of 334 end-use products (out of 592) had the same hazard categories for oral and dermal toxicity. For the purpose of this assessment, end-use products falling into Category 5 (LD_{50} = 2000-5000 mg/kg bw) and "unclassified" (LD_{50} >5000 mg/kg bw) were grouped together and were considered to have the same hazard category. This grouping was based on the lack of difference in labelling requirements between these categories under the GHS system (that is, both categories do not require label symbols or hazard statements). The oral hazard category was lower (that is, more potent) than the dermal hazard category for 256 end-use products (out of 592). Similar to the analysis using the PMRA hazard category system, there were two end-use products with a lower dermal category (that is, greater potency) than the oral category in the analysis under GHS.

The findings indicate that, regardless of the categorization system used, hazard labelling based on the acute oral toxicity study would have been protective of acute dermal toxicity for >99.5% of end-use products. That is, the data from the oral study either predicted the same hazard category as the dermal study or led to an over-prediction of dermal hazard. Less than 0.5% of end-use products had a lower (more potent) dermal hazard category compared to the oral category.

4.0 Retrospective Analysis – Active Ingredients

The results of the end-use product analysis prompted a similar analysis to be conducted by the PMRA on the acute oral and dermal rat toxicity studies for the active ingredients alone; however, it is noted that the active ingredient analysis extended beyond the scope of the RCC initiative. A retrospective analysis of the active ingredients was performed to determine if the acute oral toxicity study was similarly predictive of dermal hazard as it is with end-use products. The dataset that was used to conduct this analysis was provided to the PMRA by NICEATM and included 298 active ingredients and their LD_{50} values from acute oral and dermal toxicity tests. The data was a compilation from USEPA documents, a peer-reviewed publication on acute toxicity testing of chemicals,[5] and public toxicity databases (for example, Hazardous Substances Data Bank, European Chemicals Agency Database).

The comparison of oral and dermal hazard categories of active ingredients using the PMRA system showed a total of 169 (out of 298) that had an oral hazard category that was the same as the dermal. The dermal hazard category was over-predicted by the oral hazard category for a total of 125 (out of 298). Four active ingredients had a lower (more potent) dermal category compared to the oral category.

[5] Creton S, Dewhurst IC, Earl LK, et al (2010). "Acutetoxicity testing of chemicals – Opportunities to avoid redundant testing and use alternative approaches." *Critical Reviews in Toxicology*, 40:1, 50-83. http://www.tandfonline.com/doi/full/10.3109/10408440903401511 accessed February 2017.

The results of the analysis on the active ingredients using the GHS category system showed similar results as with the analysis on the PMRA hazard category system. The oral and dermal hazard category was the same for 155 active ingredients (out of 298). The oral hazard category over-predicted the dermal hazard category for 133 active ingredients (out of 298). Ten active ingredients had a lower (more potent) dermal category compared to the oral category.

Regardless of whether the PMRA or GHS hazard categorization system was used, hazard labelling based on the acute oral toxicity study would have been protective of acute dermal toxicity for >96% of active ingredients. Less than 4% of active ingredients had a lower (more potent) dermal category compared to the oral category. Although the level of prediction was lower than that seen in the end-use product analysis, it still represented an adequate level to support the waiver of the acute dermal toxicity study.

5.0 Implications of the Retrospective Analysis on the Acute Dermal Toxicity Study Requirement

The findings of the retrospective analysis suggest that acute oral toxicity studies on pesticide end-use products and active ingredients are a suitable alternative to predicting dermal hazard for labelling purposes. Using the oral hazard category as a predictor for dermal hazard, >99.5% of end-use products and >96% of active ingredients would have had the same or a more conservative dermal hazard category and, therefore, would have had protective hazard labelling.

6.0 Conclusion

The analysis supports the removal of the requirement for acute dermal toxicity studies for pesticide end-use products and active ingredients. The acute dermal toxicity study will remain as a conditional requirement for rare circumstances (for instance, new technology or unique characteristics) that would warrant a more comprehensive assessment of acute dermal hazard for labelling purposes.

Appendix I

Comments were received from stakeholders representing the plant science industry, registrants and an animal welfare organization. All commenters were supportive of the proposal to remove the routine requirement of acute dermal toxicity studies for pesticide end-use products and active ingredients.

Two commenters requested clarification of the circumstances under which an acute dermal toxicity study would be required. The PMRA would like to re-iterate that this study would only be required in rare circumstances. Although it is hard to predict such circumstances, it is the PMRA's intent to only invoke this requirement in the event that there is uncertainty as to whether a new technology or unique characteristic would bring into question the applicability of the retrospective analysis. For instance, the use of nanotechnology to engineer a product may impart unique characteristics of dermal absorption not reflected in the retrospective analysis. In such cases, registrants and applicants still have the opportunity to submit a scientifically supported waiver rationale for the required study. Thus, to retain flexibility for such unforeseen scenarios, the PMRA has retained the original wording in the document as follows: "The acute dermal toxicity study will remain as a conditional requirement for rare circumstances (for instance, new technology or unique characteristics) that would warrant a more comprehensive assessment of acute dermal hazard for labelling purposes."